REMARKS/ARGUMENTS

I. Status of the Prosecution

Applicants wish to thank the Examiner for consideration of the references submitted on Form 1449A. Applicants also thank the Examiner for acknowledging the election of claims 1-10. Claims 1-10 are currently pending and under examination.

Claim 1 has been amended herein to clarify the claimed invention and not for purposes related to patentability. The amendment does not narrow the scope of the claim.

II. The Claims are Novel and Nonobvious Over the Cited Art.

Claims 1-10 stand rejected under 35 U.S.C. § 35 U.S.C. § 103(a) as allegedly unpatentable over either Bertelli *et al.* (U.S. Patent Application No: 2003/0073132 A1) or Johns *et al.* (WO 00/20450) in view of Gotti *et al.* (Differentiation, 34: 144-155, 1987).

The Office Action alleges that at column 1, paragraphs 12 -26, Bertelli *et al.* teach, a method for screening compounds wherein an α2δ subunit of the Ca^{2+} channel is contacted with a compound of interest and a labeled compound, such as [^{3}H]gabapentin, and the level of binding of the labeled compound is measured with and without the compound of interest. The Office Action also alleges that at page 9, lines 24-31, Johns *et al.* teach a method wherein an α2δ subunit polypeptide is contacted with a compound of interest and wherein the complexes formed between the polypeptide and the compound of interest. The method of Johns *et al.* may further comprise administering a compound, such as gabapentin, that competes for binding with the α2δ subunit polypeptide. The effect of the compound on the binding of the competing compound,

e.g. gabapentin, is measured – a teaching at page 10 lines 10-30 and page 11, line 2 according to the Office Action.

The Office Action acknowledges that neither Bertelli *et al.* nor Johns *et al.* teach a method wherein the sample containing the α2δ subunit polypeptide is a neuroblastoma cell.

The Office Action alleges that, at pages 144 and 153, Gotti *et al.* teach that neuroblastoma IMR-32 cells incubated with BrdU have an effect on voltage-dependent channels, including Ca^{2+} channels. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to use a sample comprising cell membranes or cell membrane fragments as a source of the voltage dependent calcium channels. The Office Action asserts that the skilled artisan would have been motivated to treat the cells with BrdU because such cells are a useful model of serotonergic cells, citing Gotti *et al.* at page 154, column 1, and that the use of these cell types would allow for the identification of compounds specific to the α2δ subunit of serotonergic cells. The Office Action thus concludes that the invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art. Applicants respectfully traverse the rejection.

When applying 35 U.S.C. § 103, the United States Patent and Trademark Office must adhere to the following:

(A) The invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability of, and the obviousness of, any combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. MPEP 2141.

Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole. MPEP 2141.02. Further, a prior art reference must be considered in it entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). The prior art must suggest the desirability of the claimed invention. MPEP 2143.01. All claim limitations must be taught or suggested by the prior art. MPEP 2143.03. *See e.g. In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed Cir. 1991). The materials on which a process is carried out must be accorded weight in determining the patentability of a process. MPEP 2116. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986).

Here, the prior art does not teach all the limitations of the claimed method, it teaches away from the claimed invention, and it uses a different starting material for one or more steps.

The instant claims are directed generally to a method of for detecting binding of a test substance to an α2δ subunit of a calcium channel comprising the steps of: contacting a neuroblastoma *cell membrane* sample comprising the α2δ subunit of a calcium channel with gabapentin and a test substance; detecting binding of the gabapentin to *the cell membrane*; and

comparing the level of binding of gabapentin to the cell membrane as compared with a control cell membrane sample lacking the test substance.

Bertelli *et al.* are cited by the Office Action for a method of screening compounds wherein an α2δ subunit of the Ca^{2+} channel is contacted with a compound of interest and a labeled compound, such as [^{3}H]gabapentin, and the level of binding of the labeled compound is measured with and without the compound of interest. Bertelli *et al.*, however, do not teach a cell membrane sample. In fact they teach away from such a sample, to a soluble secreted form of the α2δ subunit instead of a cell membrane form. For example, Bertelli *et al.* teach:

> "The most frequently used assay currently available for the screening of liganeds that bind the α2δ subunit involve the use of pig membrane extracts as a source of the α2δ subunit. Such an assay presents major inconvenience. Firstly, because the assay material is a membrane extract it is very difficult to accurately determine the protein composition from one assay preparation to another particularly with regard to the subtype. Also the presence of various impurities in the assay preparation is a problem in small plate assays. Furthermore, as the protein preparation lacks homogeneity, the interaction between the targeted protein and the assay plate is often quite uneven. This renders the streamlining of the assay in a high throughput format almost impossible to achieve.
>
> The inventors have that it was possible to use a soluble secreted form of a voltage-dependant [sic] calcium channel α2δ-1 subunit polypeptide. . .in an assay for the screening of ligands which bind the α2δ-1 subunit."

See column 1, paragraphs [0005-6].

Thus, Bertelli *et al.* cannot form a basis for a *prima facie* case even in combination with Gotti *et al.* as even together they do not teach each and every limitation of the invention when considered as a whole. Not only do Bertelli *et al.* teach away from cell membranes, but they *require* contacting a *secreted soluble* α2δ subunit polypeptide with a ligand. Furthermore, Gotti *et al.* cannot serve to bolster the *prima facie* case, nor provide what Bertelli *et al.* lack. Gotti *et*

al. teach neuroblastoma cells, specifically IMR32 cells, can be proposed as a model of serotonergic cells. Applicants respectfully submit that this is insufficient motivation to combine references, especially where, as here, the claims do not contain any limitation directed to potential serotonergic properties of the cells. One of skill in the art seeking to solve the same problem (development of an assay for compounds related to binding α2δ subunit polypeptide) solved by the Applicants would not be motivated to use neuroblastoma cells because of their proposed serotonergic properties as that is motivation to solve a completely different problem. Further, as stated above Gotti *et al.* cannot provide what Bertelli *et al.* lack because Gotti *et al.* do not teach Ca^{2+} channels, particularly voltage-dependent Ca^{2+} channels, nor binding of any compounds to the α2δ subunit polypeptide of such channels. Gotti *et al.* do suggest a role in differentiation for Na^{+} and K^{+} currents, and suggest Ca2+-activated K^{+} channels (see cited page 153 and page 151), and voltage-dependent Na^{+} channels (see cited page 144 and page 154) may be involved. These teachings cannot motivate one of skill to attempt the claimed methods, nor do they provide the limitations missing from Bertelli *et al.*

With respect to Johns *et al.*, as is admitted, neither the reference as a whole nor the cited portions teach any assays using neuroblastoma cells. The Office Action takes the position that it would have been obvious to one of skill in the art to use the assays of Johns *et al.* in neuroblastoma cells. Applicants respectfully submit that this is contrary to the teachings and purpose of Johns *et al.* Johns *et al.* teach isolated nucleic acid encoding α2δ subunit polypeptides. They also teach transient expression of these nucleic acids in cell systems for use in assays. One of skill in the art seeking to use the teachings of Johns *et al.* would not be

motivated to use neuroblastoma cells, rather, the skilled artisan would be motivated to clone new α2δ subunits based on the sequences provided, or perhaps to find cells lines, like COS7, which can be readily manipulated for expression of the nucleic acids encoding the α2δ subunits to study the cloned polypeptides using the methods provided. There is no teaching or suggestion in Johns *et al.* to use those α2δ subunit polypeptides which are natively expressed, e.g. as part of voltage-dependent calcium channels in any cell type, and it is contrary to the purpose for which Johns *et al.* was developed. Johns *et al.* teach methods practiced on transiently transfected cells expressing cloned genes encoding α2δ subunits – this is a completely different problem from that of measuring gabapentin binding to cells or differentiated cells expressing native α2δ subunits. For the reasons cited above, there is no motivation to use neuroblastoma cells. Further, since as discussed above, Gotti *et al.* do not provide any teaching or suggestion of the claimed methods, particularly with respect the α2δ subunit of the voltage-dependent calcium channels, there can be no motivation for combining these references found in either of the references themselves. Any combination in the absence of a "specific hint or suggestion in a particular reference" is thus necessarily the result of impermissible hindsight and is not a proper basis for a *prima facie* of obviousness. *In re Sang Su Lee*.

Accordingly, in view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 35 U.S.C. § 103.

III. The Claims are Definite With Respect to Cell Membrane

Claims 1-9 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite because claim 1, step (b) recites the limitation "the cell membrane." The Office Action asserts that is unclear whether this limitation refers to the binding of the gabapentin to the α2δ subunit of the cell membrane sample or the binding of gabapentin to the cell membrane itself. Applicants respectfully traverse this requirement.

Applicants respectfully submit that the ordinarily skilled artisan would plainly understand the claim term as it is written. The method as a whole is also readily understood from the perspective of a skilled practitioner. It is clear from the specification that gabapentin is used as a specific ligand for the α2δ subunit of calcium channels. *See e.g.* Applicants Specification page 7, lines 15-16. *See also* Figures.

Step (b) of claim 1 recites the limitation of "detecting binding of the gabapentin to the cell membranes" from which Applicants respectfully assert the skilled artisan would readily appreciate (from the claim itself and from the claim read in view of the specification) that what is being detected is the binding of gabapentin to the "cell membranes" – which is indicative of, or a measurement of, binding to the α2δ subunit. The limits of language prevent claiming the alternative "detecting binding of gabapentin to the α2δ subunit" because this is not the actual detection step which is performed in the method, as is readily understood by one of ordinary skill in the art. It would be misleading and thus indefinite to suggest that binding to the α2δ subunit must specifically be detected, although the method as a whole is clearly determining binding to the α2δ subunit of the calcium channel.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

IV. Conclusion

Applicants believe the amendments and arguments presented herein are fully responsive to the Office Action. Applicants respectfully submit that all of the claims are in condition for allowance and early and favorable action in that regard are earnestly solicited. The Examiner is invited to contact the Applicants' undersigned representative to resolve any matters leading to the proper issuance of Applicants' claims.

Respectfully submitted,

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